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(54) Diastereomer salt of optically active quinolinemevalonic acid

Diastereomeres Salz von optisch aktiver Chinolinmevalonsäure

Sel diastéréomère d'acide quinolinemévalonique optiquement actif

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(56) References cited:
EP-A- 304 063
EP-A- 409 281
EP-A- 411 420
EP-A- 430 129
DE-A- 3 905 908
US-A- 4 567 289

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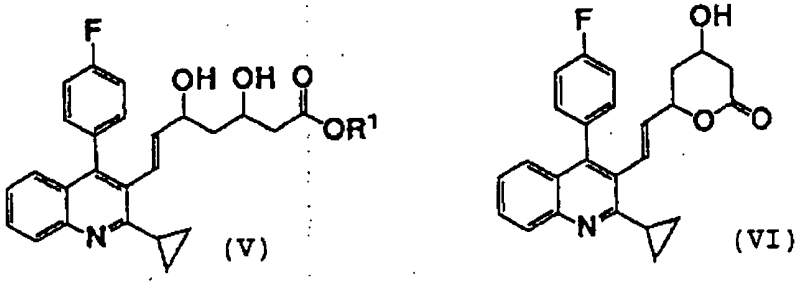
Description

The present invention relates to an important intermediate for the preparation of optically active quinolinemevalonic acid derivatives useful for the prevention or treatment of hyperlipemia, arteriosclerosis, etc. and a method for optically resolution thereof.

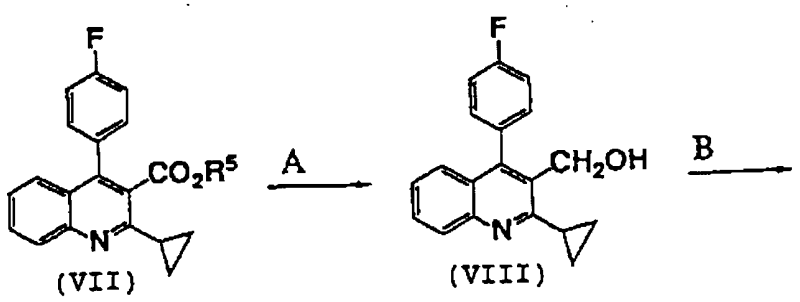
A quinolinemevalonic acid compound of the formula (V) and a quinolinemevalonolactone compound of the formula (VI):

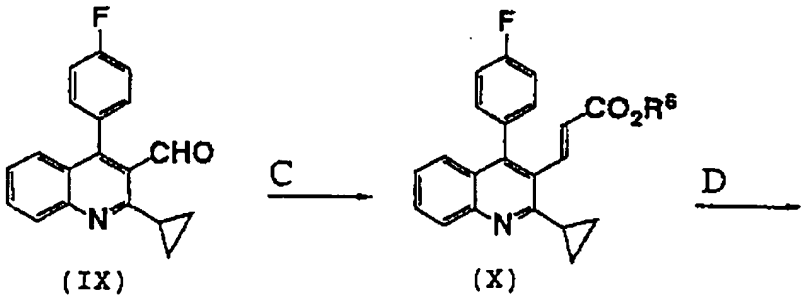


wherein R^1 is a hydrogen atom, a C_{1-4} lower alkyl group such as a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a t-butyl group, a n-butyl group, an i-butyl group, a s-butyl group, or Na, K, 1/2Ca or $HNR^2R^3R^4$ wherein each of R^2, R^3 and R^4 is hydrogen, a C_{1-3} lower alkyl group or a 2-hydroxyethyl group, or when R^2 is hydrogen or methyl, R^3 and R^4 together form $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NH-(CH_2)_2-$, are racemic mixtures or compounds having four optical isomers, as disclosed in Japanese and European Unexamined Patent Publication Nos. 279866/1989 and 304063, and they are strong inhibitors against HMG-CoA reductase which is a rate limiting enzyme for the biosynthesis of cholesterol and thus expected to be useful as drugs for the prevention and treatment of hyperlipemia, arteriosclerosis, etc.

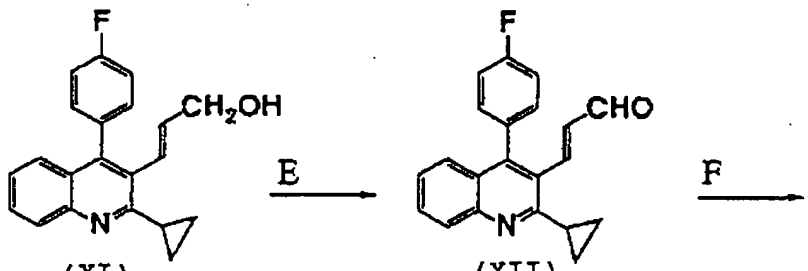
Further, quinolinecarboxylic acid derivatives as HMG-CoA reductase inhibitors are disclosed, for example, in the following literatures: German Patent DE-3905908, U.S. Patent 4,761,419, U.S. Patent 4,923,861 and European Patent Publication EP 356788A.

As disclosed in Japanese and European Unexamined Patent Publication Nos. 279866/1989 and 304063, the compounds of the formulas (V) and (VI) can be prepared as follows:

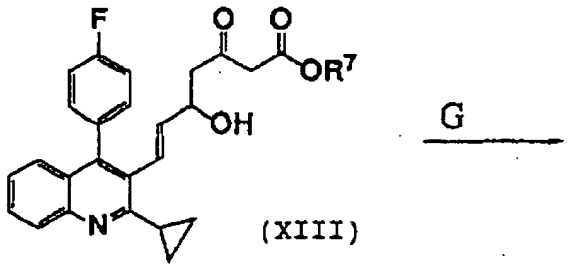




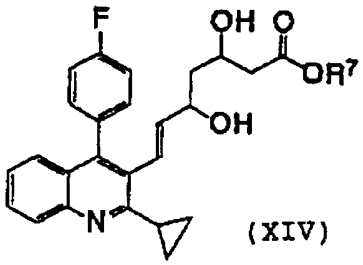
(IX) (X)



(XI) (XII)

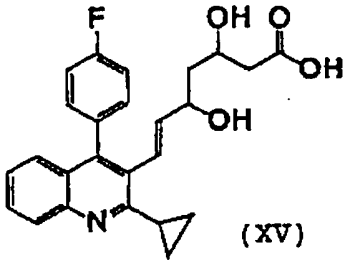


(XIII)



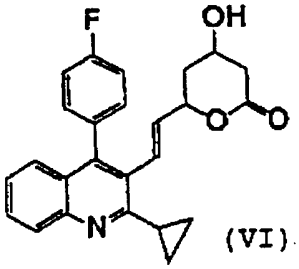
(XIV)

H



(XV)

J



(VI)

In the above formulas, each of R^5, R^6 and R^7 is a C_{1-4} lower alkyl group such as a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a t-butyl group, a n-butyl group, an i-butyl group or a s-butyl group.

Step A is a reduction reaction of an ester (VII) to a primary alcohol (VIII), and the reaction can be conducted in a solvent such as tetrahydrofuran or toluene at a temperature of from -20°C to 20°C, preferably from -10°C to 10°C, using various metal hydrides, preferably diisobutylaluminum hydride.

Step B is an oxidation reaction of the primary alcohol (VIII) to an aldehyde (IX), and the reaction can be conducted using various oxidizing agents. Preferred is a method wherein oxidation is conducted at a temperature of from 0°C to 25°C using pyridinium chlorochromate in methylene chloride, a method wherein oxidation is conducted using oxalyl chloride, dimethyl sulfoxide and a tertiary amine (such as triethylamine) (Swern oxidation), a method wherein oxidation is conducted using phosphorus pentoxide, dimethyl sulfoxide and a tertiary amine (such as triethylamine) or a method wherein oxidation is conducted using sulfur trioxide-pyridine complex.

Step C is a reaction for the preparation of an α,β-unsaturated carboxylic acid ester (X), whereby a transform α,β-unsaturated carboxylic acid ester (X) can be obtained by so-called Horner-Wittig reaction using an alkoxycarbonylmethyl phosphonate. As the base, sodium hydride, potassium-t-butoxide or the like is employed, and the reaction is conducted in dry tetrahydrofuran at a temperature of from -30°C to 0°C, preferably from -20°C to -15°C.

Step D is a reduction reaction of the α,β-unsaturated carboxylic acid ester (X) to an allyl alcohol (XI), and the reaction can be conducted in a solvent such as dry tetrahydrofuran or toluene at a temperature of from -10°C to 10°C, pref-

erably from -10°C to 0°C, using various metal hydrides, preferably diisobutylaluminum hydride.

Step E is an oxidation reaction of the allyl alcohol (XI) to an enal (XII), and the reaction is conducted using various oxidizing agents. Preferred is a method wherein oxidation is conducted in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperature of from 0°C to 100°C, preferably from 15°C to 50°C, using activated manganese dioxide, a method wherein oxidation is conducted using a sulfur trioxide-pyridine complex, a method wherein oxidation is conducted using phosphorus pentoxide, dimethylsulfoxide and a tertiary amine (such as triethyl amine), or more preferably a method wherein oxidation is conducted using oxalyl chloride, dimethyl sulfoxide and a tertiary amine (such as triethylamine) (Swern oxidation).

Step F is a condensation reaction of the enal (XII) and a double anion of an acetoacetate, and the reaction is preferably conducted in tetrahydrofuran at a temperature of from -80°C to 20°C, preferably from -30°C to 0°C, using sodium hydride as the base and n-butyl lithium.

Step G is a reduction reaction of the carbonyl group of the compound (XIII). There is a method wherein the reduction is conducted in ethanol at a temperature of from -10°C to 5°C using a metal hydride, preferably sodium borohydride, a method wherein the reduction is conducted in dry ether or dry tetrahydrofuran at a temperature of from -100°C to 25°C, preferably from -80°C to -50°C using zinc borohydride, and more preferably a method wherein the reduction is conducted in dry tetrahydrofuran-methanol at a temperature of from -80°C to -60°C using sodium borohydride and triethylborane or diethylmethoxyborane. (The compound (XIV) corresponds to the compound (V) wherein R^1 is a C_{1-4} lower alkyl group.)

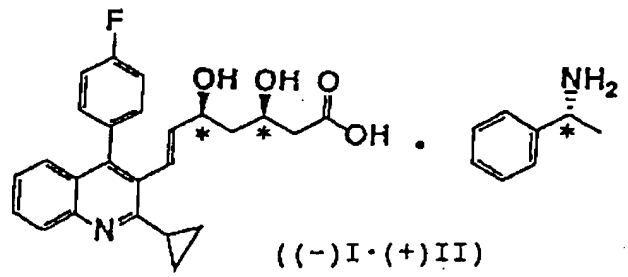
Step H is a step for hydroryzing the ester (XIV), which can be conducted in a solvent mixture of methanol or ethanol with water at a temperature of from 10°C to 25°C using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide. (The compound (XV) corresponds to the compound (V) wherein R^1 is a hydrogen atom.)

Step J is a step for forming mevalonolactone by a dehydration reaction of the free hydroxy acid (XV), and the reaction can be conducted using a suitable acid catalyst, preferably trifluoroacetic acid. Otherwise, the reaction can be conducted by removing the resulting water while refluxing in benzene or toluene under heating, or by adding a suitable water-removing agent such as molecular sieves. Further, the reaction can be conducted at a temperature of from 10°C to 35°C, preferably from 20°C to 25°C, using a lactone-modifying agent in dry methylene chloride, such as a carbodiimide, preferably a water-soluble carbodiimide such as N-cyclohexyl-N'-[2'-(methylmorpholinium)ethyl]carbodiimide p-toluenesulfonate.

With respect to drugs, there are many cases in which the pharmacological activities and safety differ among optical isomers. In order to develop an excellent drug, it is desired to separate them by optical resolution. DE-A-3 905 908 describes theoretically a method of resolution via the amide with phenethylamine. However, even given this theoretical suggestion, there has been no method for optical resolution known to be industrially useful for the separation of the racemic modification of the quinolinemevalonic acid ((±)I).

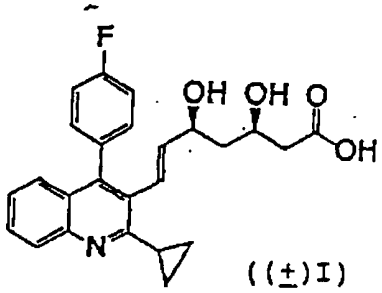
The present inventors have discovered that the racemic modification of quinolinemevalonic acid ((±)I) forms a salt with D(+) phenethylamine ((+)II) as an optically active amine, whereby the optically active quinolinemevalonic acid ((-)I) can be separated by optical resolution. The present invention has been accomplished on the basis of this discovery.

Thus, the present invention provides a diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I • (+)II):

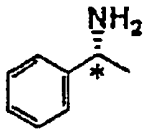


((-)I • (+)II)

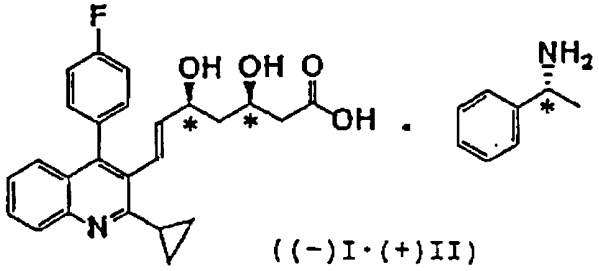
The present invention provides also a method for optical resolution of quinolinemevalonic acid ((±)I) with D(+) phenethylamine of the formula ((+)II), in a ketone-type solvent, or toluene or xylene, or a solvent mixture of such a solvent with an alcohol solvent, or dimethylformamide or dimethyl sulfoxide, or dichloromethane, and crystallizing the resulting diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I-(+)II), in a ketone-type solvent, or toluene or xylene, or a solvent mixture of such a solvent with an alcohol solvent, or dimethylformamide,dimethyl sulfoxide:



((±)I)

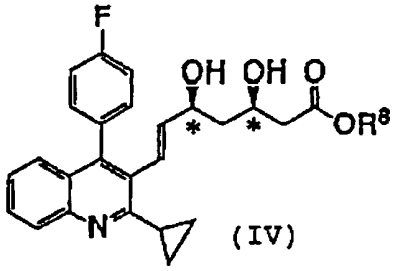


((+)II)



((-)I·(+)II)

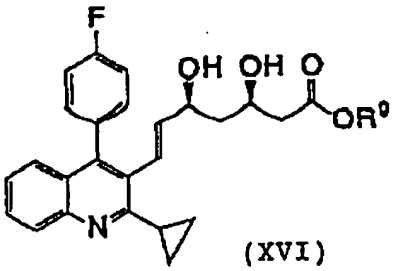
The present invention further provides a process for producing optically active quinolinemevalonic acid salt of the formula (IV)



(IV)

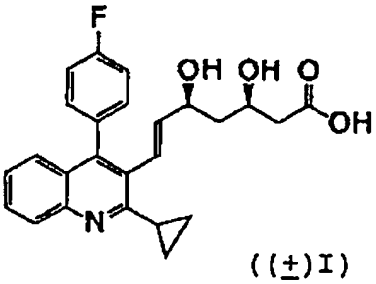
wherein R^8 is Na, K, 1/2Ca or $HNR^2R^3R^4$ wherein each of R^2, R^3, R^4 is hydrogen, a C_{1-3} lower alkyl group or a 2-hydroxyethyl group, or when R^2 is hydrogen or a methyl group, R^3 and R^4 together form $-(CH_2)_4-$, $-(CH_2)5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NH-(CH_2)_2-$, which comprises reacting the diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I·(+)II) as defined above, with a base.

Now, the present invention will be described in detail with reference to the preferred embodiments.

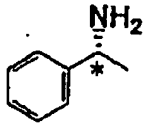


(XVI)

K



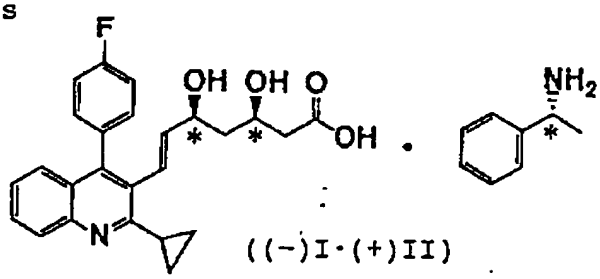
((±)I)



((+)II)

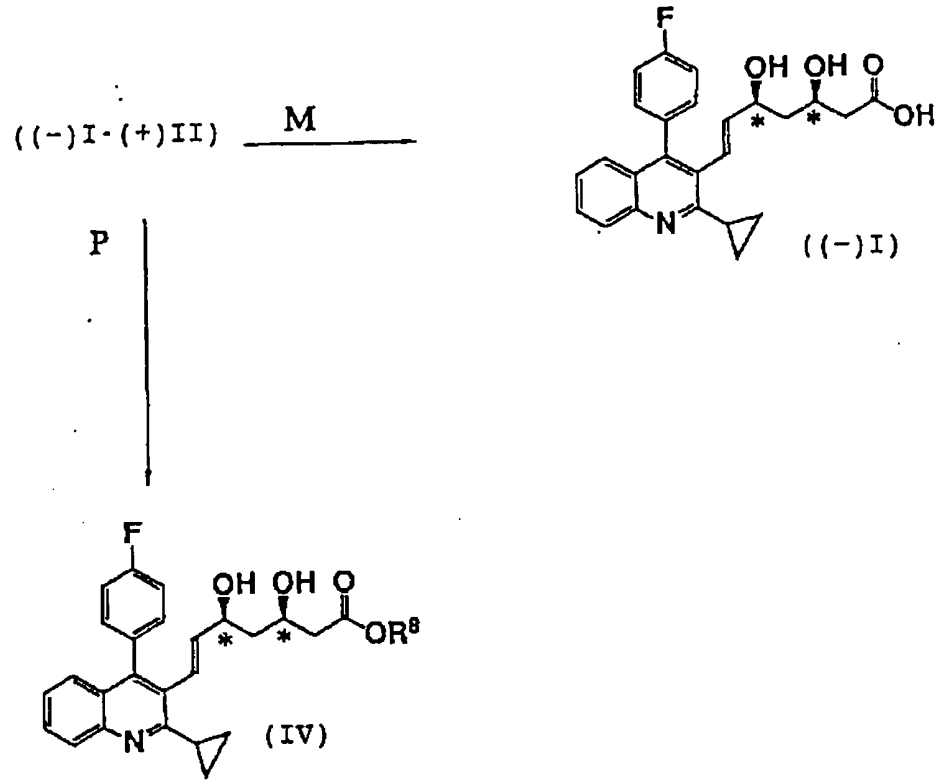
L

Crystals



((-)I·(+)II)

Mother liquor
((+)I·(+)II)



In the above formulas, R^8 is Na, K, 1/2Ca or $HNR^2R^3R^4$ wherein each of R^2, R^3 and R^4 is hydrogen, a C_{1-3} lower alkyl group or a 2-hydroxyethyl group, or when R^2 is hydrogen or methyl, R^3 and R^4 together form $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NH-(CH_2)_2-$, and R^9 is a C_{1-4} lower alkyl group.

Step K is a step for hydrolyzing a racemic ester (XVI), and the hydrolysis can be conducted in a solvent mixture of methanol or ethanol with water at a temperature of from 0°C to 25°C using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, followed by neutralization using an aqueous acid solution, preferably hydrochloric acid, to obtain a free quinoline mevalonic acid ((±)I).

Step L is a step for reacting D(+) phenethylamine ((+)II) as an optical resolution agent to the quinolinemevalonic acid ((±)I) for precipitation to obtain the diastereomer salt of optically active quinolinemevalonic acid ((-)I • (+)II) as crystals. Likewise, if L(-)phenethylamine((-)II) is used as an optical resolution agent, it is possible to obtain a diastereomer salt of optically active quinoline mevalonic acid ((+)I • (-)II). Thus, by selecting the optical resolution agent, a desired optical isomer of the quinolinemevalonic acid ((±)I) can be obtained. As the solvent, a ketone-type solvent such as diethyl ketone or methyl isobutyl ketone, or toluene or xylene is used alone, or a solvent mixture of such a solvent with an alcohol solvent such as methanol or ethanol, or dimethylformamide or dimethyl sulfoxide, is used. The reaction temperature is usually from 0°C to 100°C, and the precipitation is conducted usually at a temperature of from -20°C to 100°C, preferably from -10°C to 80°C.

In step M, the optically active quinolinemevalonic acid ((-)I) can readily be obtained by treating the diastereomer salt of optically active quinolinemevalonic acid ((-)I • (+)II) with various aqueous acid solutions. As the acid, formic acid, trifluoroacetic acid or hydrochloric acid is preferred. Particularly preferred is hydrochloric acid.

In step P, the optically active quinolinemevalonic acid salt (IV) can be obtained from the diastereomer salt of optically active quinolinemevalonic acid ((-)I • (+)II) without isolating the optically active quinolinemevalonic acid ((-)I). Namely, by adding an aqueous solution of alkali metal hydroxide (such as sodium hydroxide or potassium hydroxide) to the diastereomer salt of optically active quinolinemevalonic acid ((-)I • (+)II), it is possible to directly obtain an alkali metal salt (such as a quinolinemevalonic acid salt (IV) wherein R^8 is Na or K). Further, by adding an aqueous solution of an alkaline earth metal chloride (such as $CaCl_2$) to such an aqueous alkali metal salt solution, it is possible to obtain an alkaline earth metal salt (such as a quinolinemevalonic acid salt (IV) wherein R^8 is 1/2Ca).

Now, the present invention will be described in detail with reference to Examples, but it should be understood that

the present invention is by no means restricted by such specific Examples.

REFERENCE EXAMPLE 1

(±)-(E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid compound ((±)I)

60 g of (±)-(E)-ethyl-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-enoate (a compound (XVI) wherein R^9 is Et) was suspended in 100 mℓ of ethanol, and 200 mℓ of a 1N sodium hydroxide aqueous solution was added thereto. As the reaction proceeded, the suspension became a uniform solution. After completion of the hydrolysis, 200 mℓ of 1N hydrochloric acid was added thereto. This reaction solution was extracted with 500 mℓ of dichloromethane to obtain the desired compound ((±)I).

H-NMR($CDCl_3$), δppm
1.0-1.1 (m, 2H), 1.3-1.4 (m, 3H), 1.5-1.6 (m, 1H), 2.3-2.4 (m, 1H), 2.51 (d, 2H, J = 6.1), 2.8-3.5 (b, 3H), 4.1-4.2 (m, 1H), 4.4-4.5 (m, 1H), 5.59 (dd, 1H, J = 6.1, J = 16.1), 6.63 (d, 1H, J = 6.1), 7.1-7.4 (m, 6H), 7.5-7.7 (m, 1H), 7.9-8.0 (m, 1H).

REFERENCE EXAMPLE 2

Resolution of a diastereomer salt using a chiral organic amine

To the dichloromethane solution of the compound ((±)I) obtained in Reference Example 1, 1 equivalent of a chiral organic amine as identified in Table 1 was added, and then the solvent was distilled off to obtain a residue containing the corresponding diastereomer salt. Except for the case where the residue was oil, the residue was dissolved under heating in ten times by weight of methyl isobutyl ketone-dimethylformamide (20:1, v/v), followed by cooling to a temperature of from 10 to 25°C for crystallization. For the optical yield, the obtained diastereomer salt was treated with an acid and then converted to lactone, and the optical yield was measured by a high performance liquid chromatography using an optical resolution column (chiraSpher, tradename, manufactured by E. Merck Company).

Resolution agent (chiral organic amine)	Chemical yield (%)	Optical yield (%ee)
D(+)phenethylamine	44	73
R(+)α-(p-tolyl)ethylamine	30[1)]	60
R(-)2-amino-1-butanol	80	0
D(-)α-phenylglycinol	-[2)]	-
(-)N-benzyl-α-phenylethylamine	-[2)]	-
(-)p-bromo-α-phenylethylamine	-[2)]	-

1) A gel substance precipitated.
2) The diastereomer salt was an oily substance.

EXAMPLE 1

(E)-3(R)-5(S)-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid • D(+) phenethylamine salt compound ((-)I • (+)II)

To the dichloromethane solution of the compound ((±)I) obtained in Reference Example 1, 16.2 g of D(+) phenethylamine ((+)II) was added, and the mixture was stirred. Then, dichloromethane was distilled off to obtain a residue. The residue was repeatedly crystallized from methyl isobutyl ketone and methyl isobutyl ketone-ethanol (10:1, v/v) to obtain 19.8 g of the desired compound ((-)I • (+)II) as white crystals. (Melting point: 144-147°C, optical purity: 97%ee.)

EXAMPLE 2

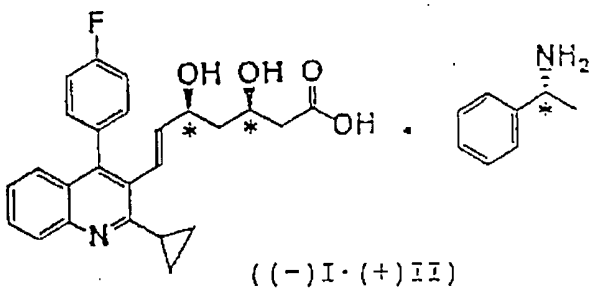
(E)-3(R)-5(S)-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid • 1/2 calcium salt

To 12.0 g of (E)-3(R)-5(S)-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid • D(+) phenethylamine salt compound ((-)I • (+)II) obtained in Example 1, 24.3 mℓ of a 1N sodium hydroxide aqueous solution and 200 mℓ of water were added and stirred to dissolve the compound. To this solution, an aqueous calcium chloride solution obtained by dissolving 1.47 g of dry calcium chloride to 200 mℓ of water, was dropwise added. This reaction solution was stirred overnight, and the resulting white precipitate was collected by filtration to obtain 9.0 g of white crystals (melting point: 190-192°C (decomposed)).

Claims

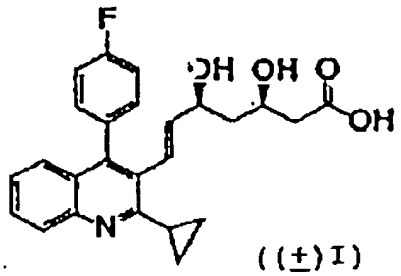
Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. A diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I • (+)II):

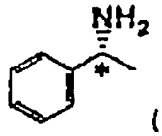


((-)I • (+)II)

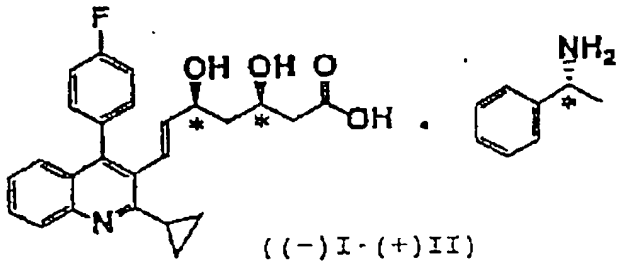
2. A method for optical resolution of quinolinemevalonic acid ((±)I), which comprises reacting the quinolinemevalonic acid of the formula ((±)I) with D(+) phenethylamine of the formula ((+)II), in a ketone-type solvent, or toluene or xylene, or a solvent mixture of such a solvent with an alcohol solvent, or dimethylformamide or dimethyl sulfoxide, or dichloromethane, and crystallizing the resulting diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I-(+)II), in a ketone-type solvent, or toluene or xylene, or a solvent mixture of such a solvent with an alcohol solvent, or dimethylformamide, dimethyl sulfoxide:



((±)I)

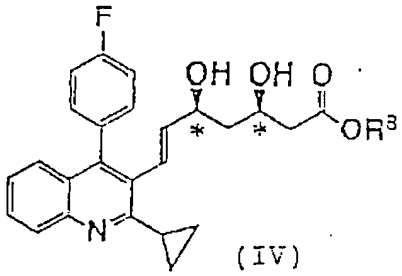


((+)II)



((-)I·(+)II)

3. A process for producing optically active quinolinemevalonic acid salt of the formula (IV)



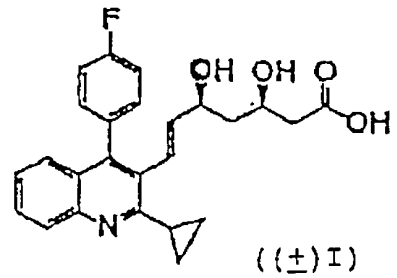
(IV)

wherein R^8 is Na, K, 1/2Ca or $HNR^2R^3R^4$ wherein each of R^2, R^3, R^4 is hydrogen, a C_{1-3} lower alkyl group or a 2-hydroxyethyl group, or when R^2 is hydrogen or a methyl group, R^3 and R^4 together form $-(CH_2)_4-$, $-(CH_2)5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NH-(CH_2)_2-$,
which comprises reacting the diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I • (+)II) as defined in Claim 1, with a base.

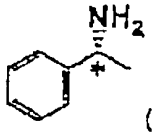
Claims for the following Contracting States : ES, GR

1. A method for optical resolution of quinolinemevalonic acid ((±)I), which comprises reacting the quinolinemevalonic acid of the formula ((±)I) with D(+) phenethylamine of the formula ((+)II), in a ketone-type solvent, or toluene or

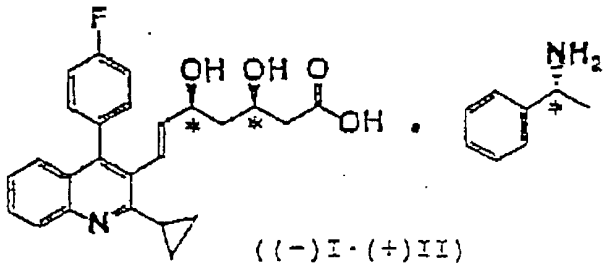
xylene, or a solvent mixture of such a solvent with an alcohol solvent, or dimethylformamide or dimethyl sulfoxide, or dichloromethane, and crystallizing the resulting diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I-(+)II), in a ketone-type solvent, or toluene or xylene, or a solvent mixture of such a solvent with an alcohol solvent, or dimethylformamide, dimethyl sulfoxide:



((±)I)

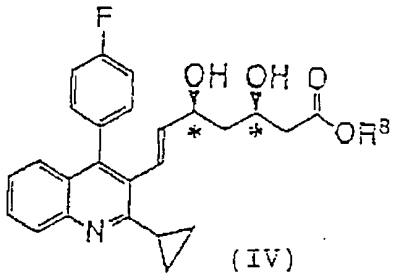


((+)II)



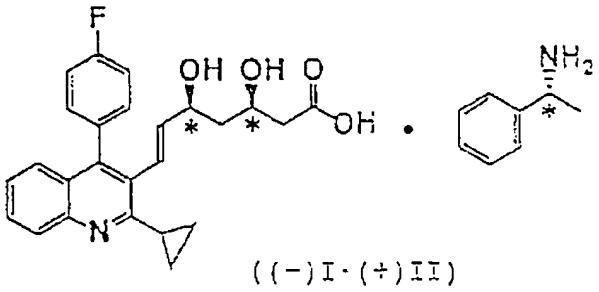
((-)I·(+)II)

2. A process for producing optically active quinolinemevalonic acid salt of the formula (IV)



(IV)

wherein R^8 is Na, K, 1/2Ca or $HNR^2R^3R^4$ wherein each of R^2, R^3, R^4 is hydrogen, a C_{1-3} lower alkyl group or a 2-hydroxyethyl group, or when R^2 is hydrogen or a methyl group, R^3 and R^4 together form $-(CH_2)_4-$, $-(CH_2)5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NH-(CH_2)_2-$,
which comprises reacting the diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I·(+)II):



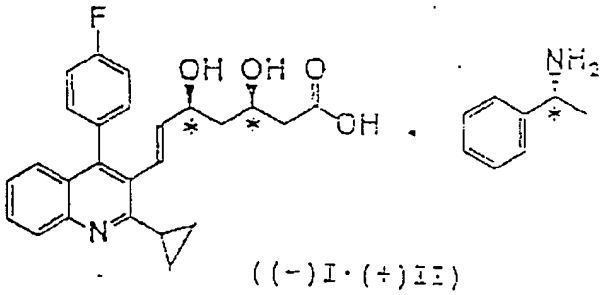
((-)I · (+)II)

with a base.

Patentansprüche

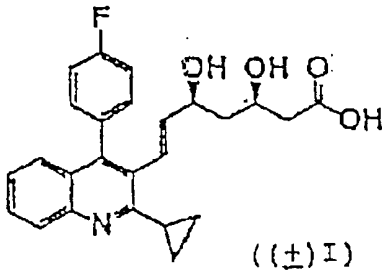
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

1. Diastereomeres Salz optisch aktiver Chinolinmevalonsäure der Formel ((-)I · (+)II):

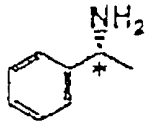


((-)I · (+)II)

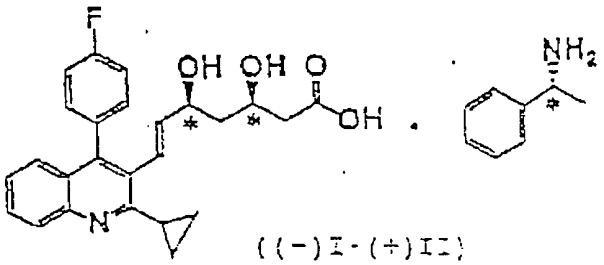
2. Verfahren zur optischen Trennung von Chinolinmevalonsäure ((±)I), umfassend das Umsetzen der Chinolinmevalonsäure der Formel ((±)I) mit D(+)-Phenethylamin der Formel ((+)II) in einem Keton-Lösungsmittel oder Toluol oder Xylol oder einer Lösungsmittel-Mischung eines solchen Lösungsmittels mit einem Alkohol-Lösungsmittel oder Dimethylformamid oder Dimethylsulfoxid oder Dichlormethan und Kristallisieren des resultierenden diastereomeren Salzes der optisch aktiven Chinolinmevalonsäure der Formel ((-)I)-(+)II) in einem Keton-Lösungsmittel oder Toluol oder Xylol oder einer Lösungsmittel-Mischung eines solchen Lösungsmittels mit einem Alkohol-Lösungsmittel oder Dimethylformamid, Dimethylsulfoxid:



((±)I)

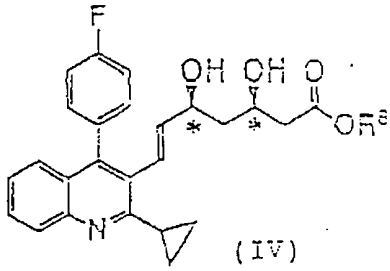


((+)II)



((-)I·(+)II)

3. Verfahren zum Herstellen optisch aktiven Chinolinmevalonsäuresalzes der Formel (IV)

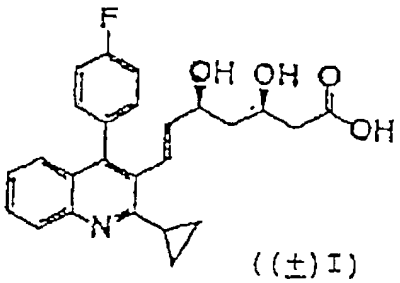


(IV)

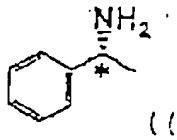
worin R^8 Na, K, 1/2 Ca oder $HNR^2R^3R^4$ ist, worin jedes von R^2, R^3, R^4 Wasserstoff, eine niedere C_{1-3}-Alkylgruppe oder eine 2-Hydroxyethylgruppe ist, oder, wenn R^2 Wasserstoff oder eine Methylgruppe ist, R^3 und R^4 zusammen $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ oder $-(CH_2)_2-NH-(CH_2)_2-$bilden, umfassend das Umsetzen des diastereomeren Salzes der optisch aktiven Chinolinmevalonsäure der Formel ((-)I•(+)II), wie es in Anspruch 1 definiert ist, mit einer Base.

Patentansprüche für folgende Vertragsstaaten : ES, GR

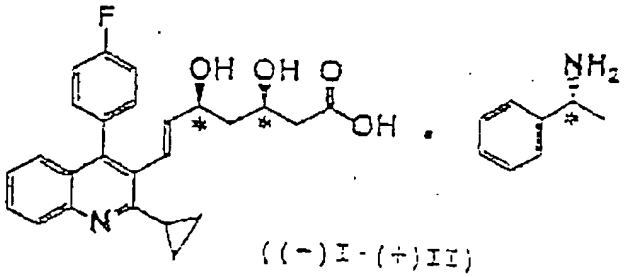
1. Verfahren zur optischen Trennung von Chinolinmevalonsäure ((±)I), umfassend das Umsetzen der Chinolinmevalonsäure der Formel ((±)I) mit D(+)-Phenethylamin der Formel ((+)II) in einem Keton-Lösungsmittel oder Toluol oder Xylol oder einer Lösungsmittel-Mischung eines solchen Lösungsmittels mit einem Alkohol-Lösungsmittel oder Dimethylformamid oder Dimethylsulfoxid oder Dichlormethan und Kristallisieren des resultierenden diastereomeren Salzes der optisch aktiven Chinolinmevalonsäure der Formel ((-)I)-(+)II) in einem Keton-Lösungsmittel oder Toluol oder Xylol oder einer Lösungsmittel-Mischung eines solchen Lösungsmittels mit einem Alkohol-Lösungsmittel oder Dimethylformamid, Dimethylsulfoxid:



((±)I)

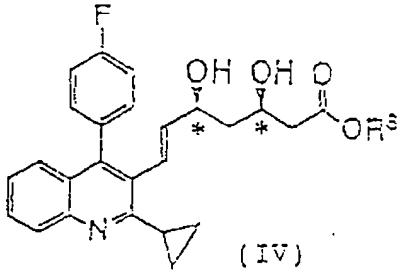


((+)II)



((-)I-(+)II)

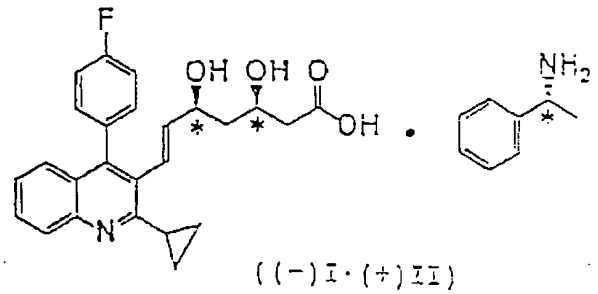
2. Verfahren zum Herstellen optisch aktiven Chinolinmevalonsäuresalzes der Formel (IV)



(IV)

worin R^8 Na, K, 1/2 Ca oder $HNR^2R^3R^4$ ist, worin jedes von R^2, R^3, R^4 Wasserstoff, eine niedere C_{1-3}-Alkylgruppe

oder eine 2-Hydroxyethylgruppe ist, oder, wenn R^2 Wasserstoff oder eine Methylgruppe ist, R^3 und R^4 zusammen $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ oder $-(CH_2)_2-NH-(CH_2)_2-$bilden, umfassend das Umsetzen des diastereomeren Salzes der optisch aktiven Chinolinmevalonsäure der Formel ((-)I • (+)II):



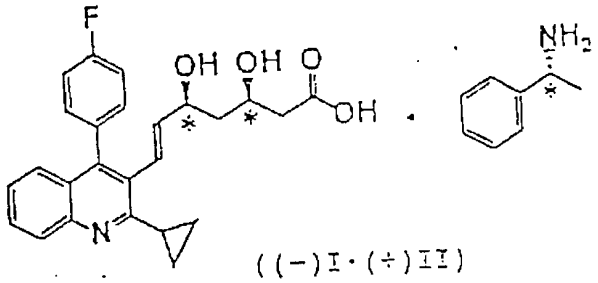
((−)I • (+)II)

mit eine Base.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, MC, NL, PT, SE

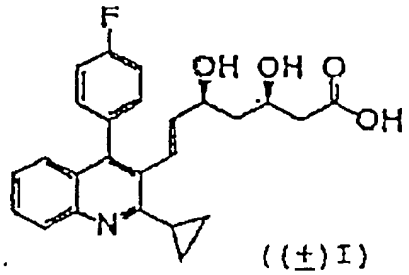
1. Sel diastéréoisomère de l'acide quinoléinemévalonique optiquement actif de formule ((-)I.(+)II) :



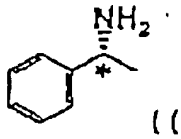
((−)I • (+)II)

2. Procédé pour le dédoublement optique de l'acide quinoléinemévalonique ((±)I), qui comprend la réaction de l'acide quinoléinemévalonique de formule ((±)I) avec la D(+)-phényléthylamine de formule ((+)II), dans un solvant de type cétone, ou dans le toluène ou le xylène, ou dans un mélange de solvants, constitué d'un tel solvant et d'un solvant alcool, ou encore dans le diméthylformamide, le diméthylsulfoxyde ou le dichlorométhane,

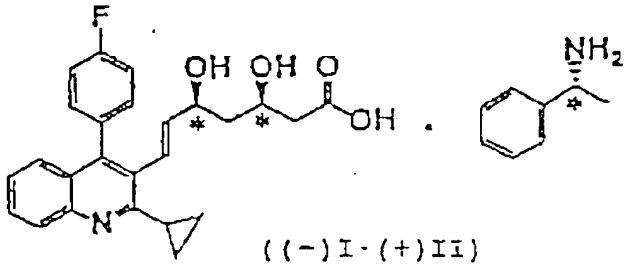
   et la cristallisation du sel diastéréoisomère obtenu de l'acide quinoléinemévalonique optiquement actif de formule ((-)I-(+)II), dans un solvant de type cétone, ou dans le toluène ou le xylène, ou dans un mélange de solvants, constitué d'un tel solvant et d'un solvant de type alcool, ou encore dans le diméthylformamide, le diméthylsulfoxyde :



((±)I)

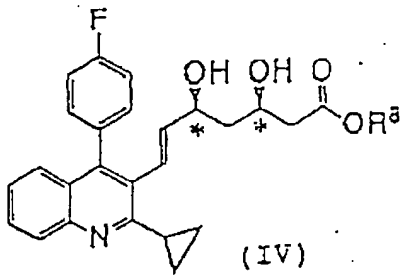


((+)II)



((-)I·(+)II)

3. Procédé pour produire un sel de l'acide qinoléinemévalonique optiquement actif de formule (IV)



(IV)

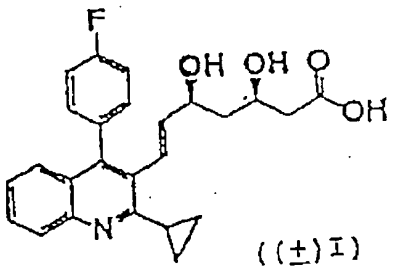
dans laquelle R^8 est Na, K, 1/2Ca ou $HNR^2R^3R^4$ où chacun de R^2, R^3, R^4 est un hydrogène, un groupe alkyle inférieur en C_{1-3} ou un groupe 2-hydroxyéthyle, ou encore, quand R^2 est un hydrogène ou un groupe méthyle, R^3 et R^4 forment ensemble $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ ou $-(CH_2)_2-NH-(CH_2)_2-$,

qui comprend la réaction du sel diastéréoisomère de l'acide quinoléinemévalonique optiquement actif de formule ((-)I.(+)II) selon la revendication 1, avec une base.

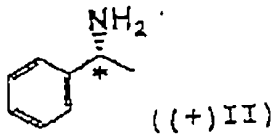
Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour le dédoublement optique de l'acide quinoléinemévalonique ((±)I), qui comprend la réaction de l'acide quinoléinemévalonique de formule ((±)I) avec la D(+)-phényléthylamine de formule ((+)II), dans un solvant de type cétone, ou dans le toluène ou le xylène ou dans un mélange de solvants, constitué d'un tel solvant et d'un solvant alcool, ou encore dans le diméthylformamide, le diméthylsulfoxyde, ou le dichlorométhane,

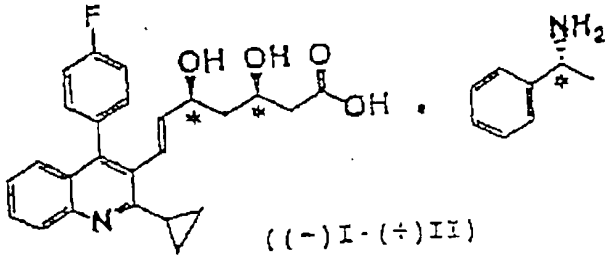
   et la cristallisation du sel diastéréoisomère obtenu de l'acide quinoléinemévalonique optiquement actif de formule
   ((-)I-(+)II), dans un solvant de type cétone, ou dans le toluène ou le xylène, ou dans un mélange de solvants, constitué d'un tel solvant et d'un solvant de type alcool, ou encore dans le diméthylformamide, le diméthylsulfoxyde :



((±)I)

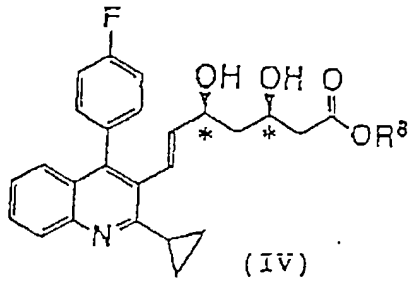


((+)II)



((-)I-(+)II)

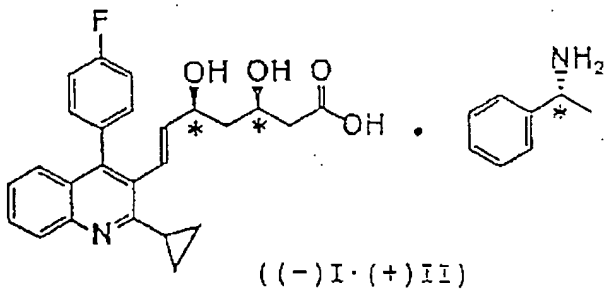
2. Procédé pour produire un sel de l'acide qinoléinemévalonique optiquement actif de formule (IV)



(IV)

dans laquelle R^8 est Na, K, 1/2Ca ou $HNR^2R^3R^4$ où chacun de R^2, R^3, R^4 est un hydrogène, un groupe alkyle inférieur en C_{1-3} ou un groupe 2-hydroxyéthyle, ou encore, quand R^2 est un hydrogène ou un groupe méthyle, R^3 et R^4 forment ensemble $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ ou $-(CH_2)_2-NH-(CH_2)_2-$,

qui comprend la réaction du sel diastéréoisomère de l'acide quinoléinemévalonique optiquement actif de formule ((-)I.(+)II) :



((-)I·(+)II)

avec une base.